International Journal of Basic and Applied Medical Sciences ISSN: 2277-2103 (Online)
An Online International Journal Available at http://www.cibtech.org/jms.htm
2013 Vol. 3 (2) May-August, pp.314-319/Javed Mulla
Research Article

ROLE OF LIPID-SOLUBLE ANTIOXIDANT & OXIDATIVE STRESS IN CARDIO-VASCULAR DISEASES IN INDIAN INDIVIDUALS

***Javed B. Mulla**
Department of Medical Biochemistry, Bharati Vidyapeeth University, Sangli
**Author for Correspondence*

ABSTRACT
α-Tocopherol is an important lipid-soluble antioxidant. It performs its functions as antioxidant in the glutathione peroxidase pathway and it protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. Extensive evidence has demonstrated that lipid-soluble antioxidant have protective effects in preventing cardiovascular disease, a chronic disease that is mediated by oxidative stress and inflammation. This review focuses on evidence from prospective cohort studies and clinical trials in regard to the associations between plasma/dietary antioxidants and cardiovascular events. Long-term, large-scale, population-based cohort studies have found that higher levels of lipid-soluble antioxidant i.e. vitamin E associated with a lower risk of CVD. However, results from large randomized controlled trials did not support long-term use of single antioxidant supplements for CVD prevention due to their null or even adverse effects on major cardiovascular events. Diet quality indexes that consider overall diet quality rather than single nutrients have been drawing increasing attention. The studies that focused on diet patterns such as high total antioxidant capacity have documented protective effects on CVD risk. A sufficient supply with antioxidants from diet might help prevent or delay the occurrence of pathological changes associated with oxidative stress. The recognition of the critical importance of oxidative stress has led to the enthusiastic use of antioxidants in the treatment and prevention of h cardiovascular disease, but the results of prospective, randomized clinical trials.This review provide a perspective for future studies that investigate antioxidant intake and risk of cardiovascular diseases.

Key Words: *Antioxidant. α-Tocopherol, Oxidative Stress, Cardiovascular Disease*

INTRODUCTION
Lipid-soluble antioxidants have been evaluated for both primary and secondary prevention of cardiovascular diseases. Studies of the mechanisms of atherosclerosis suggest that antioxidants might be protective. Observational studies appeared to show benefits with higher intake of some antioxidants. Additionally, cardiovascular protection has been associated with dietary patterns high in antioxidants (from fruit and vegetables) (Dauchet, 2006) and with higher circulating levels of alpha tocopherol (Wright, 2006) However, most randomized, controlled trials have not found antioxidant supplementation to be effective for the prevention of CVD. Cardiovascular disease is the most common cause of death in India and accounts for approximately one third of all deaths around the world. In this paper we will overview some of the details of our emerging understanding of inflammation and its principal source, oxidative stress. Further, we will critically review the historical advocacy of antioxidants for the treatment and prevention of inflammatory-initiating oxidative stress, and proffer explanations for the failure to date of antioxidants to achieve therapeutic success. Finally, we will discuss the appropriateness of oxidative stress as a therapeutic target in cardiovascular disease (Münzel, 2010). Multiple factors are involved in the cause of CVD, including fixed factors (gene, age, gender), and modifiable factors (diet, smoking, environment, exercise). Formation of an atherosclerotic plaque or lesion is the common phenomenon of all types of CVD. The initiating step in the development of an atherosclerotic lesion is damage to the endothelium (Huang, 2010). Oxidative stress and inflammation are key mechanistic pathways involved in endothelial dysfunction and thus atherosclerosis, which will be discussed in the following. Diet, as an important modifiable factor ameliorating CVD risk, is a health target in the public health field. This

review focuses on evidence from prospective cohort studies and clinical trials in regard to the associations between plasma/dietary antioxidants and cardiovascular events.

MATERIALS AND METHODS

We manually searched epidemiologic studies of antioxidants in relation to CVD risk published between 2000 and 2012 in Pub Med. Antioxidant and CVD were used as key words for searching. Inclusion criteria included large-scale cohort studies and intervention trials in human and dietary or plasma antioxidants as exposures. Dietary antioxidants including vitamin E, α-Tocopherol and total antioxidant capacity (TAC) were selected because both cohort studies and intervention studies have been conducted on these antioxidants. Plasma/serum antioxidants selected as endogenous antioxidants included vitamin E, tocopherol. TAC is an emerging biomarker of overall antioxidant status and was also included. Eligible outcomes were CVD incidence and CVD death for vitamin E, tocopherol and TAC as exposures due to limited studies on CVD incidence or mortality.

RESULTS AND DISCUSSION

Recently, progress has been made regarding the source of the oxidative stress and an understanding has been achieved regarding the role of the signaling cascade that moderates the resulting inflammatory process. Oxygen free radicals, also termed reactive oxygen species (ROS) (Traber, 2007), are molecules that contain one or more unpaired electrons and singlet oxygen. ROS are highly reactive and damaging to cells due to the unpaired electrons. The consequence is that new free radicals produced attack healthy cells and thus a chain reaction occurs. An imbalance between ROS and antioxidants in favor of the former is defined as oxidative stress (Herrera, 2001). Oxidative stress is one of the causative factors that have long been identified as being involved in the pathogenesis of CVD as well as many other degenerative diseases such as cancer, and immune dysfunction (Hopps, 2009). However, as far back as the late 1940's (and perhaps before), antioxidants such as vitamin E have been suggested as potentially useful in the treatment of cardiovascular disease (Salone, 2000). Studies on the inhibition of experimental cholesterol arteriosclerosis in animals were published around 1949-1950 and specific discussions of the use of vitamin E in the treatment of cardiovascular disease appeared the same year. Over the years an oxidative stress hypothesis supported by epidemiologic and observational evidence that encouraged belief in and the use of antioxidants (Boaz, 2000). For example, studies of fruit and vegetable consumption, those particularly rich in vitamin E and other antioxidants, correlated with a reduction in CVD mortality (Ching, 2002). Further, the plasma level of vitamin E was inversely related to mortality from ischemic heart disease (Novotny, 2003). Inflammation is a key factor in all aspects of cardiovascular disease including the initiation and progression of atherosclerotic plaque, plaque rupture, and thrombosis (atherothrombosis), especially in recurrent thrombosis where oxidative stress is known to play a significant role (Ceconi, 2003) including in those with normal cholesterol levels and in those being treated with "statins" and antiplatelet agents. This inflammation, caused by oxidative stress, could be a target for a great next wave of cardiovascular therapeutics.

Antioxidants are molecules that could give electrons to oxidants thus stop the chain reactions. Human bodies are equipped with a powerful antioxidant defense system that controls deleterious reactions of ROS, Thus, plasma antioxidants that exhibit antioxidant/anti-inflammatory effects have been associated with a lower risk of CVD. Tocopherols, forms of vitamin E, are chain-breaking lipophilic compounds that exist in human plasma and LDL in four isoforms (α-tocopherol, γ-tocopherol, β-tocopherol, and δ-tocopherol). Although γ-tocopherol is the major form of vitamin E in diet, α-tocopherol has the highest bioavailability. Despite α-tocopherol has lower oxygen quenching rates than carotenoids, the higher plasma level of α-tocopherol brings its oxygen quenching capacities up to comparable magnitudes with lycopene and β-carotene **(**Kromhou, 2005).Several large-scale, prospective cohort studies have focused on the relationship between plasma/serum antioxidant molecules and CVD as summarized in Table 1.

Table 1: Cohort studies on plasma levels of antioxidants and the risk for cardiovascular events

Exposures	Study population characteristics	Follow-up (year)	Outcomes	RR (highest *vs.* lowest) and 95% CI, *p*-trend
Vitamin E	725 men and women, ≥60 years	9–12	HD mortality	1.51 (0.68–3.37), 0.15
α-Tocopherol	1168 men and women, 70–75 years	10	CVD mortality	0.83 (0.67–1.03)
α-Tocopherol	29,092 male smokers, 50–69 years	19	CVD mortality	0.81 (0.75–0.88) *, <0.0001

Intake of fruits and vegetables has long been associated with a lower risk for several chronic diseases mediated by oxidative stress, including CVD. Dietary antioxidants such as vitamin E, Tocopherols, and polyphenols were thought to responsible for the cardiovascular protective effect through suppressing oxidative stress suggested by preclinical studies and epidemiological studies. However, large-scale, randomized controlled trials in human did not support this hypothesis. Although the cause of this paradox was unknown, inherent confounding in epidemiological studies and different physical conditions in study populations may partly explain it. To get some clues through comparing previous studies, evidence from prospective studies and randomized controlled trials were reviewed and summarized in Tables 2 and 3

Table 2: Cohort studies on dietary intake of antioxidants and the risk for cardiovascular events

Exposures	Study, country, year	Study population characteristics	Follow-up (year)	Outcomes	RR (highest *vs.* lowest) and 95% CI, *p*-trend
Vitamin E: T, D, S	NHS [61], USA 1993	87,245 female nurses, 34–59 years	8	CHD (nonfatal MI + fatal CHD)	T: 0.66 (0.50–0.87) *, <0.001 D: 0.95(0.72–1.23), 0.99 S > 2 years: 0.59 (0.38–0.91) *
Vitamin E: T, D, S	HPFS [62], USA 1993	39,910 male health professionals, 40–75 years	4	CHD (nonfatal MI + fatal CHD + CABG + PTCA)	T: 0.64 (0.49–0.83) *, <0.001 D: 0.79 (0.54–1.15), 0.11 S: 0.7 (0.55–0.89) *, 0.22
Vitamin E	FMCS [63], Finland 1994	5133 men and women, 30–69 years	14	CHD mortality	M: 0.68 (0.42–1.11), <0.05 F: 0.35 (0.14–0.88) *, <0.01
Vitamin E: T	NMR [33], USA 1996	725 men and women, ≥60 years	9–12	HD mortality	0.75 (0.41–1.39), 0.40

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) cohort consisted of 29,092 male smokers aged 50–69 years old. After a follow-up period of 19 years, men in the highest quintile of serum α-tocopherol had a 19% lower risk (relative risk (RR): 0.81; 95% confidence interval (CI): 0.75, 0.88) for death due to CVD compared with men from the first quintile.Other studies did not find significant or similar results.

Table 3: Randomized controlled trials of supplemental intake of antioxidants and the risk for cardiovascular events

Treatment, dose	Study name	Follow-up (year)	Study population characteristics	Type	Outcomes	RR (treatment *vs.* placebo) and 95% CI
Vitamin E, 800 or 400 UI/day	CHAOS [81], 1996	1.4	2002 men and women, mean age 62 years, with coronary disease	Secondary	Nonfatal MI + CVD mortality	0.53 (0.34–0.83) *
Vitamin E, 50 mg/day	ATBC [82], Finland 1997	5.3	1862 male smokers with MI history	Secondary	Nonfatal MI + fatal CHD	Null outcome
Nonfatal MI						0.62 (0.41–0.96) *
Fatal CHD						Null outcome
Vitamin E, 50 mg/day	ATBC [83], Finland 2000	6	28,519 male smokers with no history of stroke	Primary	Stoke (SH, IH, CI) incidence and mortality	SH mortality: 2.81 (1.37–5.79) * CI incidence: 0.86 (0.75–0.99) *
Vitamin E, 400 IU/day	HOPE [84], Canada 2000	4.5	9541 men and women, ≥55 years, at high risk of CVD	Primary and Secondary	MI + stroke + CVD mortality	Null outcome

The effects of dietary vitamin E intake on CVD risk have been investigated by several large cohort studies. An inverse association between dietary total vitamin E intake and heart disease risk was reported by several studies (Vivekananthan, 2003**)** though findings were controversial when a vitamin E supplement was used. Health Professionals Follow-Up Study (HPFS) found higher total vitamin E intake and ≥100 IU/day vitamin E supplement use were inversely associated with CHD in men. After an 8 year follow-up, total vitamin E intake and vitamin E from supplements were not associated with risk of CHD mortality, but vitamin E from food was inversely associated with CHD mortality (*p*trend = 0.004), with women in the highest quintile of vitamin E intake having a 62% lower risk (RR: 0.38; 95% CI: 0.18, 0.80) of CHD compared with those in the lowest quintile. Previously reviewed large cohort studies have suggested that antioxidant vitamins, especially vitamin E, tocopherol may reduce CVD risk. Accordingly, these vitamin supplements were widely tested in several large-scale, randomized controlled trials to

investigate their protective effects against CVD risk. However, surprisingly null or even adverse results have been reported as summarized in Table 3. Null results on combined CVD endpoints were reported by several primary or secondary prevention trials. Three studies, including the Cambridge Heart Antioxidant Study (CHAOS) and Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) reported protective effects of vitamin E supplementation on combined CVD endpoints. Adverse effects of vitamin E supplementation were reported in three studies including the recently published PHS-II. In this study, 14,641 middle-aged or older male physicians with or without a baseline history of CVD were followed for 8 years. Supplement of 400 IU vitamin E every other day had no effects on major cardiovascular events and even increased hemorrhagic stroke by 74% (RR:1.74; 95%CI: 1.04, 2.91 (Dzau, 2006). Overall the results of antioxidant supplement randomized clinical trials were disappointing. The null or adverse results did not support long-term use of dietary antioxidant supplement for CVD prevention (Lonn, 2005). Although the underlying mechanisms for the null or adverse effects are still not well known, some design points are worth discussing and improvement in future studies. In terms of supplement dose, the non-linear relationships between antioxidant intake and disease risks indicate that a cut-off value exists for optimal health for some antioxidants. High dose of antioxidant intake may result in toxicity to human bodies (Stanner, 2004). Most of the antioxidants such as vitamin E, carotenoids, and uric acid can play a role as oxidants *in vivo* at their high concentrations. In addition, competitive inhibition may exist with a high dose of a single antioxidant. Different physical conditions and family CVD history of the participants might also.

It is concluded that antioxidant supplement use was reported to have no effect or an adverse effect on cardiovascular events by several large randomized controlled trials, cohort studies still supported the protective effects of dietary antioxidants on preventing CVD. Besides antioxidant vitamins E, tocopherol is a large group of compounds that exhibit high antioxidant capacity *in vitro* and cardioprotective effects *in vivo*. Although the *in vivo* effects of tocopherol may be beyond the scope of the topic-antioxidants of this review, considering the synergistic effect between antioxidants, dietary quality scores, and dietary TAC that considered the overall diet quality are still worth investigating with regard to the association between diet and CVD.

ACKNOWLEDGEMENT

Authors are grateful to Medical College and Hospital, Sangli for providing facility to conduct this study.

REFERENCES

Boaz M and Smetana S (2000). Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial, *The Lancet* **356**(9237) 1213–1218.

Ceconi C and Boraso A (2003). Oxidative stress in cardiovascular disease: Myth or fact? *Archives of Biochemistry and Biophysics* **420** 217–221.

Ching S and Ingram D (2002). Serum levels of micronutrients, antioxidants and total antioxidant status predict risk of breast cancer in a case control study. *Journal of Nutrition* **132** 303–306.

Dauchet L, Amouyel P, Hercberg S and Dallongeville J (2006). Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *Journal of Nutrition* 136-2588.

Dzau VJ and Black HR (2006). The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: Pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease) Circulation **114**(25) 2850–2870.

Herrera and Barbas C (2001). Vitamin E: action, metabolism and perspectives. *Journal of Physiology and Biochemistry* **57**(2) 43–56.

Hopps E *et al.*, (2009). A novel component of the metabolic syndrome: the oxidative stress, *Nutrition, Metabolism and Cardiovascular Diseases* **20**(1) 72–77.

Huang W and Glass CK (2010). Nuclear receptors and inflammation control: molecular mechanisms and pathophysiological relevance. *Arteriosclerosis, Thrombosis, and Vascular Biology* **30**(8) 1542–1549.

Kromhou FJ and Groot LC (2005). Plasma carotene and alpha-tocopherol in relation to 10-y all-cause and cause-specific mortality in European elderly: The Survey in Europe on Nutrition and the Elderly, a Concerted Action (SENECA). *American Journal of Clinical Nutrition* **82** 879–886.

Lonn E and Bosch J (2005). Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *JAMA* **293** 1338–1347.

Münzel T and Taddei S (2010). Is oxidative stress a therapeutic target in cardiovascular disease? *European Heart Journal* **31**(22) 2741–2749.

Novotny L and Vitek L (2003). Inverse relationship between serum bilirubin and atherosclerosis in men: A meta-analysis of published studies. *Experimental Biology and Medicine* **228** 568–571.

Salone JT and Nyyssonen K (2000). Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis, *Journal of Internal Medicine* **248(**5) 377–386.

Stanner SA and Hughes J (2004). A review of the epidemiological evidence for the 'antioxidant hypothesis', Public Health Nutrition **7**(3)407–422.

Traber and Atkinson J (2007). Vitamin E, Antioxidant and Nothing More. *Free Radical Biology and Medicine* **43**(1) 4–15.

Vivekananthan DP and Penn MS (2003). Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials, *The Lancet* **361**(9374) 2017–2023.

Wright ME and Lawson KA (2006). Higher serum concentrations of vitamin E are associated with lower total and cause-specific mortality in α -Tocopherol, Cancer Prevention Study. *American Journal of Clinical Nutrition* 84-1200.